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Aminopyridines for symptomatic treatment in multiple sclerosis (Review)

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[Intervention Review]

Aminopyridines for symptomatic treatment in multiple sclerosis

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ABSTRACT

Background

The potassium channel blockers 4-aminopyridine (AP) and 3,4-diaminopyridine (DAP) increase nerve conduction in demyelinated nerve fibers, and have been proposed as a symptomatic therapy for people with multiple sclerosis (MS).

Objectives

To determine the efficacy and safety of aminopyridines for neurological deficits in adults with MS.

Search methods

We searched the Cochrane MS Group trials register (December 2004), the Cochrane Central Register of Controlled Trials (The Cochrane Library Issue 4, 2004), MEDLINE (January 1966 to December 2004) and EMBASE (1974 to December 2004). We hand searched bibliographic references from retrieved studies and recent MS symposia reports, and contacted known studies' investigators.

Selection criteria

We included trials fulfilling all following criteria: randomised controlled trials (RCTs); adults with MS, out of exacerbation; AP or DAP treatment versus placebo; clinical endpoints.

Data collection and analysis

Three reviewers independently extracted data and assessed trial quality from 17 full-paper studies.

Main results

Six studies (eight publications, 198 participants, all crossover trials) were considered. Five studies assessed the efficacy of AP versus placebo, one compared DAP with active placebo. Treatment duration ranged from hours to six months. Median quality score of the studies was three.

Of the 198 treated participants, there were six major side effects: one acute encephalopathy, three episodes of confusion, and two seizures. Three studies (54 participants) assessed manual muscle testing, with 29 participants (54%) improving in at least one muscular district during study treatment versus four participants (7%) during placebo (odds ratio [OR] 14.5, 95% confidence interval [CI] 4.7 to 43.7). Nine out of 54 participants (17%) improved in ambulation during study treatment versus none during placebo ($p < 0.001$). A lower Expanded Disability Status Scale (EDSS) score was found in 13/198 participants during study treatment (7%) versus none during placebo ($p < 0.001$).

No improvement in neuropsychological tests was found in three trials assessing cognitive function. Finally, 47/136 adults with MS (35%) felt better when receiving the study drug, against 7(5%) on placebo (OR 9.7, 95% CI 4.3 to 22.0).

Authors' conclusions

Currently available information allows no unbiased statement about safety or efficacy of aminopyridines for treating MS symptoms. Furthermore, we could not obtain any data on three unpublished RCTs (more than 300 participants). We conclude that publication bias remains a pervasive problem in this area, and that until the results of these unpublished studies are available to the scientific community, no confident estimate of effectiveness of aminopyridines in the management of MS symptoms is possible.

PLAIN LANGUAGE SUMMARY

The effect of aminopyridine for the treatment of several symptoms in people with multiple sclerosis

Multiple sclerosis (MS) is a disease that affects young and middle-aged adults, causing different symptoms in individuals. It is caused by damage to the myelin sheaths (fibres that wrap around and protect the nerves and spinal cord). Potassium (a mineral) is important for nerve function, but may become too active when there is not enough myelin. Potassium blocking drugs (4-aminopyridine AP, and 3,4-daminopyridine DAP) may be able to improve nerve function in nerves without enough myelin. However, the review of trials found there is not enough evidence about the safety of these drugs or whether benefits are certain.

BACKGROUND

Multiple sclerosis (MS) is the most important non-traumatic cause of neurological disability in young adults. Although MS etiology and pathogenesis remain imperfectly understood it is widely believed that the disease has an immune-mediated basis and occurs in genetically susceptible individuals. Inflammation and demyelination of the central nervous system are considered the main features of the disease (Prineas 1978). More recently, substantial axonal damage has also been demonstrated by means of pathological and imaging studies (McDonald 1992; Narayanan 1997; Trapp 1998).

Despite advances in treatments that apparently have curative action, so far no intervention has proven effective in modifying long-term disease prognosis. Therefore symptomatic and supportive therapies remain important in the management of the various clinical manifestations of MS.

The potassium channel blockers 4-aminopyridine (AP) and 3,4-diaminopyridine (DAP) have been proposed as symptomatic therapies for MS; their mechanism of action is reviewed here reviewed briefly. During action potential propagation in a normal myelinated axon, sodium channels that are clustered in high density at the nodes of Ranvier open transiently, causing the action potential to jump from one node to the next (saltatory conduction). The internodal part of the axon is covered by myelin and contains fewer sodium channels but a higher density of potassium channels, which tend to oppose the generation of action potentials (Waxman 1996). In demyelinated axons potassium channels appear on the axolemma and decrease action potential amplitude and duration. Potassium channel blockers increase action potential amplitude and duration thus improving nerve conduction in experimentally demyelinated animal nerves (Bostock 1978; Sherrat 1980). An alternative mechanism of action has been recently proposed for AP; in experimentally demyelinated dorsal axons of rats the drug potentiates synaptic transmission and increases skeletal muscle twitch tension (Smith 2000). Over the last 10 years several RCT with AP and DAP in MS patients have been published, and the drugs have been proposed as effective symptomatic treatments, especially in temperature-sensitive patients (Bever 1994b; Davis 1990; Stefoski 1991). DAP has also been proposed as a symptomatic treatment in patients with Lambert-Eaton myasthenic syndrome (McEvoy 1989). A number of side effects have also been reported, the most serious of which is the occurrence of seizures (Bever 1994b; Polman 1994a). Several approaches to minimizing aminopyridine toxicity have been proposed, such as finding a molecular analogue associated with fewer side effects and the best-tolerated formulation (i.e. sustained release preparations)(Bever 1995b; Schwid 1997).

A previously published review on aminopyridines in MS did not follow the formal rules of systematic overview (Bever 1994a); furthermore publication bias may limit interpretation of studies in this area: most RCTs have been relatively small, and a large completed *negative* study has not been published (Pogue 1998).

OBJECTIVES

To determine the efficacy and safety of the aminopyridines AP and DAP in improving neurological deficits in MS patients.

The secondary objectives were subgroup analyses considering the molecule (AP or DAP), and type of preparation (regular or sustained release).

METHODS

Criteria for considering studies for this review

Types of studies

RCTs of AP or DAP versus placebo (either inert or active, e.g. nicotinic acid) were identified and considered for inclusion in the review. Truly randomised crossover studies were also included (i.e. crossover studies in which the sequence of treatment assignment was randomly allocated). Uncontrolled trials and controlled studies where the intervention was compared with other therapies were not included. Studies comparing DAP with AP were also excluded.

Types of participants

Clinically definite (Poser or other internationally recognised classification criteria) MS patients aged 18 years or more of either sex. Patients in exacerbation were excluded.

Types of interventions

Both AP and DAP versus placebo, given in any dose, route, or formulation (including sustained release) were considered. In studies where more than one dosage was compared to control treatment, all patients receiving the study intervention were aggregated, for the purposes of this review, into a single group. Subgroup analyses considering the molecule (AP or DAP), and type of preparation (regular or sustained release) were also considered.

Types of outcome measures

The main events of interest were:

(1) Safety assessment: the number of dropouts and incidence of adverse events. Adverse events were categorised into (a) mild/moderate and (b) major events (death, seizures or any event requiring hospitalisation or medical treatment).

(2) Changes in disability or impairment scales assessing: (a) motor function, (b) visual acuity, (c) cognition, and (d) fatigue.

(3) Quality of life.

(4) Patients' subjective response.

Isolated neurophysiological improvement was not considered.

Outcomes were assessed overall, acutely (hours), and intermediately (at four weeks). The proportion of patients improved on the predefined outcome measures were also reported.

We sought to extract from each RCT the number of patients originally assigned to each treatment group so as to allow an intention-to-treat analysis, if the trial had not already been presented in this way.

Search methods for identification of studies

The databases were searched to locate publications written in English, French, German, Italian or Dutch.

Electronic searches

(1) Cochrane MS Group Trials Register (December 2004)

(2) Cochrane Central Register of Controlled Trials (CENTRAL) "The Cochrane Library Issue 4,2004"(Appendix 1)

(3) MEDLINE (from January 1966 to December 2004)(Appendix 2)

(4) EMBASE (from 1974 to December 2004)(Appendix 3)

Searching other resources

(5) Reference lists of all available review articles and primary studies found by running the above mentioned databases.
(6) Handsearch of recent (1997 to 2002) symposia reports from the most important national neurological associations and MS societies in Europe and America.
(7) Contact with researchers participating in trials on aminopyridines.
(8) Inquiry to Elan/Acorda Pharmaceutical Research Corporation.

Data collection and analysis

Study Selection

Three reviewers (AS, CT, BU) independently screened titles, abstracts, and descriptors of all studies identified by the search strategy and discarded irrelevant publications to create a list of eligible studies. After the potential trials and reviews had been retrieved, each reviewer independently applied the eligibility/exclusion criteria to unblinded full reports.

Data Extraction

The reviewer extracted from each study the following information, which was abstracted onto a predefined form: inclusion/exclusion criteria; number of participants excluded from the trial (not enrolled for logistical reasons, refused consent, not eligible); description of randomisation; description of the study and control treatment; description of blinding of treatment administration and of outcome assessment; definition of efficacy and safety endpoints; length of follow-up; number of participants withdrawn from or dropping out of the trial after randomisation; number of participants with incomplete follow-up; intention-to-treat analysis (whether performed or could be done); pre trial specification/justification of sample size; and testing for period and carry-over effects (cross-over studies only). Both interim analyses and final results were considered. There was no disagreement on study inclusion between authors.

Assessment of Study Quality

All three reviewers independently assessed the methodological quality of eligible trials published as full papers using the Jadad checklist (Jadad 1996). The reviewers were not blinded to the names of the authors, institutions, journal, or study results. The Jadad scale consists of three items: description of randomisation, blinding, and attrition. The scale score ranges from zero (lowest possible score) to five (highest possible score), with two points given for description of randomisation and blinding, and one point given for description of attrition. Studies scoring less than three points are generally regarded as being of low methodological quality. For cross-over studies, we added an additional item assessing the washout period: one additional point was deducted from the global Jadad score if the washout period was not described, there was no washout period, or if the washout was described but considered inappropriate by the reviewer.
Inter-rater agreement on methodological quality scale scores was assessed by means of the kappa statistic. The kappa coefficient takes into account and corrects for chance-explained agreement; it ranges between zero (completely chance-explained agreement) and one (perfect agreement) (Fleiss 1971; Landis 1977).

RESULTS

Description of studies

Electronic and manual searches identified 74 titles and abstracts. Of these, 47 were considered non pertinent. Of the remaining 27 references, one was a narrative overview (Bever 1994a); three were dose-finding or tolerability studies (Bever 1990; Bever 1995a; Bever 1995b) and one was a duplicate publication (Bever 1995b). Five studies were case series (Bertelsmann 1992; Polman 1994a; Fujihara 1998; Landete 1998; Sheean 1998); four were non randomised studies (Jones 1983; Stefoski 1987; Davis 1990; Stefoski 1991); and 13 were RCTs. Five references were excluded since they were duplicate studies (van Diemen 1993a; de Waal 1994; Smits 1994b; Rossini 1996a; Rossini 1996b), one was an AP versus DAP comparative trial (Polman 1994b), and one was excluded since only paraclinical endpoints were considered (van Diemen 1993b), in the same participants to a previously published study (van Diemen 1992). Of the remaining seven trials, one was an abstract and no detailed results have been published over the 12 years (Carter 1993), and six were full-text articles (van Diemen 1992; Bever 1994b; Smits 1994a; Bever 1996; Schwid 1997; Rossini 2001). One paper of Van Diemen (van Diemen 1993a) was in two parts, one being a duplicate (part II) and the other evaluating eye movements in the same patients reported in a previous publication (van Diemen 1992). Consequently this publication is considered both among included (part I) and excluded studies (part II). In the table of excluded studies however we could not report van Diemen 1993a, part II, since a single reference can not be reported two times, i.e. among both included and excluded studies. The reader should consider this point when examining the table and the reference of excluded studies, which should include also van Diemen 1993a, part II. All eligible RCTs had a crossover design; in no instance was information on the individual study period given.
Three unpublished trials were also identified by contact with trialists and by searching the National MS Society publication of clinical trials of new agents in MS.
In spring 1999 we contacted the principal investigators of all the included RCTs, and principal investigators/pharmaceutical company sponsor of unpublished studies. For the published trials, an extraction form was also enclosed. Four to six months, and also one year later, each investigator was contacted again. We have so far received answers from the authors of four studies, expressing their willingness to give the information requested (van Diemen 1992; van Diemen 1993a; Polman 1994b; Smits 1994a). *Elan/Acorda* also answered our second request, stating: "Our policy is not to release specific data pertaining to our clinical trials prior to their publication".

This review is based on a total of six studies (seven publications) that were randomised, placebo-controlled, double-blind trials. There is one more abstract awaiting assessment.
All studies were single centre crossover trials. Five studies assessed the efficacy of AP versus placebo. The daily dose of AP ranged from up to 40 mg (Smits 1994a)] to up to 100 mg (Bever 1994b). One study was a double cross-over comparing placebo with low dose and high dose AP (Bever 1994b). One study assessed the efficacy of DAP versus nicotinic acid (active placebo) (Bever 1996). Duration of treatment ranged from hours (van Diemen 1993a; Bever 1994b) to six months (Rossini 2001). Safety was assessed in all studies from clinical side effects, and by means of routine laboratory testing (van

Diemen 1992; Bever 1994b; Rossini 2001), ECG (Bever 1994b; Rossini 2001) and EEG changes (van Diemen 1992; Bever 1994b).

All six studies assessed several efficacy outcomes. These included overall measures of impairment and disability (van Diemen 1992; Smits 1994a; Bever 1994b; Bever 1996; Schwid 1997; Rossini 2001)], quantitative motor testing (Bever 1994b; Bever 1996; Schwid 1997), fatigue (Rossini 2001), visual testing (van Diemen 1992; Bever 1994b; Rossini 2001) eye movement registration (van Diemen 1992; van Diemen 1993a), neuropsychological testing (Smits 1994a; Bever 1996; Rossini 2001), neurophysiological testing (Rossini 2001), fatigue (Rossini 2001), and patients' subjective impressions (van Diemen 1992; Smits 1994a; Bever 1996; Schwid 1997). Primary study endpoints were specified a priori in four trials (van Diemen 1992; Smits 1994a; Bever 1996; Rossini 2001).

Risk of bias in included studies

Three observers (AS, CT, BU) independently assessed the quality of the included trials. The inter-rater agreement on 16 full paper articles was almost perfect for items assessing whether the study was randomised, whether it was double blind, and on the appropriateness of the washout period (Table 1). Moderate agreement was found for appropriateness of the randomisation method, and for withdrawal/dropout reporting. The kappa value for the appropriateness of double blinding was close to zero. This finding is the result of imbalance in marginal totals distribution in the concordance table, and has been described in the literature (Feinstein 1990). To overcome this problem, the proportion of agreement in the raters' positive and negative judgments is also reported in the table, and indicated as P(pos) and P(neg).

The median quality score of the seven included publications (six studies) was three (range two to five). The randomisation method was reported in only one study (Schwid 1997). All the studies were double blind, and the blinding was described in all of them. Withdrawals and dropouts were described in five publications (Bever 1996; Schwid 1997; van Diemen 1992; van Diemen 1993a; Rossini 2001). Washout was described and considered appropriate in two papers (Bever 1996; Schwid 1997). One study had no washout period (Rossini 2001).

Effects of interventions

At this point therefore, this review is based on six RCTs (198 participants) reported in seven full-paper articles. All the included studies were single institution, double blind, crossover RCTs. Three were from the US, two from the Netherlands and one was an Italian study. Because of lack of information on the individual periods of the studies, we could not enter the data into MetaView. It was in fact possible to perform only a limited number of comparisons of categorical outcomes, and for all these comparisons, events were reported for aggregated periods only (i.e. treatment or placebo phases). In no instance was information given on the number of participants achieving a specific outcome in a specific phase. No trial was excluded on the basis of quality score. A short summary of the main findings of the six studies is reported in table form. The following data were also calculated on the basis of information given in the original published papers:

Safety

Among the 198 treated patients, six major side effects were reported: one acute encephalopathy (Bever 1994b), three episodes of confusion (Bever 1994b), and two seizures (Bever 1994b; Bever 1996). Four major side effects were reported in 36 people with MS during treatment with DAP (11%) (Bever 1996), and two during AP treatment (1%). Both epileptic fits were tonic-clonic seizures in persons with no history of epilepsy or loss of consciousness. One episode was reported on DAP treatment, and the other during AP treatment, when serum AP packed at 104 ng/ml. Withdrawals and dropouts were reported in all six studies, with 18 attritions in 162 participants treated with AP (11%) (van Diemen 1992; van Diemen 1993a; Schwid 1997; Rossini 2001), and eight attritions in 36 participants treated with DAP (22%) (Bever 1996). No participant was lost to follow up. Finally, in 46% (32 participants) of a group of participants treated with intravenous AP, side effects were considered the reason to stop the infusion (van Diemen 1993a).

Motor function

Three RCTs (54 participants) considered motor function testing as study outcome (Bever 1994b; Bever 1996; Schwid 1997). Manual muscle testing was performed in all the studies considered, with 29 participants (54%) improving in at least one district during study treatment versus four participants (7%) during placebo (odds ratio [OR] 14.5, 95% confidence interval [CI] 4.75 to 43.72, $p < 0.001$).

Eye movements

Two trials assessed eye movement by means of smooth pursuit gain recordings (van Diemen 1992; van Diemen 1993a). The two studies evaluated this parameter in 70 participants after intravenous infusion of AP (van Diemen 1993a), and also over a three-month oral administration period (van Diemen 1992; van Diemen 1993a). The authors found mean improvements in smooth pursuit gain in both eyes during both acute and prolonged treatment with AP (data not shown).

Ambulation

Three studies (54 patients) assessed the efficacy of aminopyridines on ambulation, which was assessed with the Ambulation Index (Bever 1994b; Bever 1996) or with timed gait (patients were judged as improved if timed gait decreased by 10 seconds or more) (Schwid 1997). Overall, nine participants (17%) improved in ambulation during study treatment versus none during placebo ($p < 0.0001$).

EDSS

All six RCTs considered Expanded Disability Status Scale (EDSS) as study outcome. An improvement in EDSS score was found in 13 participants during study treatment (7%) versus none during placebo ($p < 0.0001$).

Visual function

Three trials assessed visual function by means of mean changes in contrast sensitivity, flicker fusion frequency, and evoked potential latencies (van Diemen 1992; Bever 1994b; Rossini 2001).Two studies also considered evoked potential amplitudes (Bever 1994b; Rossini 2001). Significant changes in favour of treatment were reported for evoked potential latency in one study (van Diemen 1992), and for contrast sensitivity in another (Bever 1994b).

Cognitive function

No improvement in neuropsychological tests was detected in three trials that evaluated cognitive function changes. Two studies employed the Brief Repeatable Battery of Neuropsychological Tests as outcome measure (Smits 1994a; Bever 1996), and the Italian trial used an ad hoc neuropsychological battery consisting in

the following tests: Auditory Attention Test, Forward Digit and Corsi's Block Span test, 15' Delayed Recall of the Rey's 15-Words List, Rey's Figure A, Phonological Word Fluency, Benton's Line Orientation Test, Token Test, Wisconsin Card Sorting Test, and Raven's Progressive Matrices (Rossini 2001). In two trials the intervention drug was oral AP (Smits 1994a; Rossini 2001), and in one it was sustained-release DAP (Bever 1996).

Fatigue
The Fatigue Severity Scale (FSS) was the prespecified primary endpoint of one study (Rossini 2001). Mean changes in the FSS did not differ between placebo and AP treatment. Investigators found a significant difference in favour of AP in participants with AP blood level > 30 ng/ml (Tukey's adjusted ANOVA, p = 0.05). It should be noted that the cut off point was selected post hoc, and the number of participants with high values (out of 31 participants in whom AP serum level was determined) was not reported.

Patients' subjective response
Patients' subjective impression was assessed in four studies (136 participants) (van Diemen 1992; Smits 1994a; Bever 1996; Schwid 1997). Overall, 47 participants (35%) felt improved when receiving the study drug, and seven participants (5%) felt improved on placebo (OR 9.73, 95% CI 4.28 to 22.05, p < 0.0001).

DISCUSSION

Our purpose was to conduct a systematic review of the safety and efficacy of aminopyridines in the management of symptoms of MS. Aminopyridines are only available as preparations specifically made up by the dispensing pharmacist. To improve tolerability and minimise side effects, *Elan/Acorda* devised an oral slow-release AP formulation and sponsored a multicenter RCT. The trial has not been published so far, and the slow-release AP formulation has not been registered.

We considered only RCTs, and all were crossover studies. Regarding safety, there were six major side effects in a total of 198 treated people with MS. This 3% frequency of serious adverse events is not negligible, especially if we consider that all the studies included narrowly defined participants (i.e., all the trials excluded people with a history of seizures, unexplained loss of consciousness, or epileptiform activity on EEG).

With regard to efficacy outcomes, since the aminopyridines are used to treat many symptoms of MS, the number of outcome considered in the studies and within a single study was high. Since few common end points were available across trials and because of lack of information on individual periods within all of the studies, none of the data could be pooled for quantitative analyses. Similarly, we could not perform any subgroup analyses considering a specific drug (AP or DAP), dosage, or formulation (regular or sustained release). Publication bias was another, and possibly more important concern. We traced three unpublished RCTs involving a planned number of 331 people with MS. It is unlikely that, irrespective of study results, any indexed journal would refuse to publish such recently performed trials that in at least two instances were well powered, multicenter trials. We therefore feel that the currently available evidence on the efficacy of AP and DAP for treating symptoms of people with MS is biased.

Publication bias is therefore the major concern of this systematic review. To note that one RCT published as an abstract has been considered among excluded studies in the most recent update since full data have not been availbe over a 12 year period (Carter 1993). Other negative aspects are the following:
(1) The benefit of aminopyridines may be overestimated in this review since in all but two trials the primary endpoint was not specified, and in such a many-outcome situation, this raises the distinct possibility of false positive findings.
(2) Furthermore, the published studies tended to include detailed data only on outcomes found to be statistically significant.
(3) When dealing with a symptomatic intervention outcomes which are meaningful to patients should be used. In no instance was quality of life considered as a study outcome, although patients' subjective response was assessed in four trials.

AUTHORS' CONCLUSIONS

Implications for practice

This review cannot provide a reliable statement concerning the efficacy of AP or DAP for treating symptoms of people with MS. A conclusion on the safety of these preparations is even more problematic due to the limited power of the current systematic review to reliably detect major adverse events, and to the low external validity of the results (narrow entry criteria).

Implications for research

There is a clear need to make available to the scientific community the results of unpublished trials on safety and efficacy of the aminopyridines in people with MS. We do not therefore conclude that more trials are needed in this area, but that these studies should be published.

ACKNOWLEDGEMENTS

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bever 1994b

Methods	Design: RCT, crossover double-blind Quality score: 2 (1/2/0/-1)
Participants	Country: USA Participants: 8 people with MS, temperature-sensitive, EDSS 3.0-8.0, with visual and lower extremity motor deficits
Interventions	Placebo, or AP 30-59 ng/ml/day PO, or AP 10-100 ng/ml/day PO
Outcomes	EFFICACY: EDSS; AI; Strength score; Videotape score; Quantitative motor testing (hamstring, quadriceps); Visual testing (contrast sensitivity, flicker fusion frequency, P100 latency). SAFETY/TOLER.: Clinical side effects; ECG; EEG; Routine blood examination; Serum AP
Notes	Observation period: 30 hours. We are attempting to contact the authors for information on each study period

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Bever 1996

Methods	Design: RCT, crossover double-blind Quality score: 4 (1/2/1/0)
Participants	Country: USA Participants: 36 people with MS
Interventions	Active placebo (nicotinic acid), or DAP up to 100 mg/day PO
Outcomes	EFFICACY: EDSS; AI; Strength score;

Bever 1996 *(Continued)*

	Videotape score; Quantitative motor testing (hamstring, quadriceps); Manual motor test score; BRBNT; Patient's subjective impression. SAFETY/TOLER: Clinical side effects; Serum DAP level
Notes	Observation period: one month We are attempting to contact the authors for information on each study period

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Rossini 2001

Methods	Design: RCT, crossover double-blind Quality score: 3
Participants	Country: Italy Participants: 54 people with MS
Interventions	Placebo, or AP 32 mg/day PO
Outcomes	EFFICACY: Fatigue Severity Scale; EDSS; neuropsychological battery (9 tests); neurophysiological evaluation (VEPs, SEPs, MEPs) SAFETY/TOLER: Clinical side effects; ECG; biological parameters; Hamilton's Depression Scale
Notes	Observation period: 6 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Schwid 1997

Methods	Design: RCT, crossover double-blind Quality score: 5 (2/2/1/0)
Participants	Country: USA Participants: 10 people with MS
Interventions	Placebo, or AP sustained-release 35 mg/day PO

Schwid 1997 *(Continued)*

Outcomes	EFFICACY: EDSS; Timed gait; Maximum voluntary isometric contraction testing; Composite manual muscle testing; Grip strength; Patient's global impression. SAFETY/TOLER: Clinical side effects
Notes	Observation period: one week We are attempting to contact the authors for information on each study period

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Smits 1994a

Methods	Design: RCT, crossover double-blind Quality score: 2 (1/2/0/-1)
Participants	Country: The Netherlands Participants: 20 people with MS
Interventions	Placebo, or AP 20-40 mg/day PO
Outcomes	EFFICACY: EDSS; BRBNT; Patients' subjective impression. SAFETY/TOLER: Clinical side effects
Notes	Observation period: 2 weeks We are attempting to contact the authors for information on each study period

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

van Diemen 1992

Methods	Design: RCT, double crossover double-blind Quality score: 3 (1/2/1/-1)
Participants	Country: The Netherlands

van Diemen 1992 *(Continued)*

	Participants: 70 people with MS , EDSS 2.0-7.5
Interventions	Placebo, or AP up to 0.5 mg/kg/day PO
Outcomes	EFFICACY: EDSS; FS; No. of relapses; Visual testing (contrast sensitivity, visual acuity, visual evoked potentials latency and amplitude); Eye movement registration (smooth pursuit gain, saccadic latencies and peak velocities); Patients' subjective impression. SAFETY/TOLER: Clinical side effects; Routine blood examination; EEG
Notes	Observation period: 3 months We are attempting to contact the authors for information on each study period

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

van Diemen 1993a

Methods	Design: RCT, double crossover double-blind Quality score: 3 (1/2/1/-1)
Participants	Country: The Netherlands Participants: 70 people with MS, EDSS 2.0-7.5
Interventions	Placebo, or AP up to 0.5 mg/kg/day IV drip (60 to 260 min.)
Outcomes	EFFICACY: Eye movement registration (smooth pursuit gain). SAFETY/TOLER: Clinical side effects; 4-Aminopyridine serum level; ECG.
Notes	Phase I study only Observation period: mean 120 min after ending infusion. We are attempting to contact the authors for information on each study period

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

AI: Ambulation Index

BRBNT: Brief repeatable battery of neuropsychological tests (selective reminding, 10/36 spatial recall - long term storage, symbol digit modalities, paced auditory serial addition, word list generation)
EDSS: Expanded Disability Status Scale
ECG: electrocardiogram
EEG: electroencephalogram
FS: Kurtzke's Functional Systems
MEPs: Motor evoked potentials
MS: multiple sclerosis
PO: per os
SEPs: sensory evoked potentials
VEPs: Visual evoked potentials

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bertelsmann 1992	Case series
Bever 1990	Dose finding/tolerability
Bever 1995a	Dose finding/tolerability
Bever 1995b	Duplicate of Bever 1995a
Carter 1993	No detailed data published nor provided by authors
Davis 1990	Non randomised study
de Waal 1994	Duplicate of Polman 1994b
Fujihara 1998	Case series
Jones 1983	Non randomised study
Landete 1998	Case series
Polman 1994a	Case series
Polman 1994b	Comparative trial (AP versus DAP)
Rossini 1996a	Duplicate of Rossini 2001
Rossini 1996b	Duplicate of Rossini 2001
Sheean 1998	Case series
Smits 1994b	Duplicate study
Stefoski 1987	Non randomised study
Stefoski 1991	Non randomised study
van Diemen 1993b	Only paraclinical end points, same patients as in van Diemen 1992

ADDITIONAL TABLES

Table 1. Interrater agreement on 17 studies published as full papers

Characteristic	P(pos)	P(neg)	Kappa	p value
Randomised study	0.56	0.42	1.00	< 0.001
Randomisation appropriateness	0.18	0.76	0.69	< 0.001
Double blind study	0.54	0.44	1.00	< 0.001
Double blinding appropriateness	0.93	0.04	-0.06	0.61
Withdrawals/dropouts	0.56	0.40	0.70	< 0.001
Washout	0.62	0.34	0.86	< 0.001

APPENDICES

Appendix 1. CENTRAL search strategy

#1 "multiple sclerosis"

#2 MeSH descriptor Multiple Sclerosis explode all trees

#3 "Demyelinating disease*"

#4 MeSH descriptor Demyelinating Diseases, this term only

#5 "transverse myelitis"

#6 MeSH descriptor Myelitis, Transverse, this term only

#7 "neuromyelitis optica"

#8 "optic neuritis"

#9 MeSH descriptor Optic Neuritis explode all trees

#10 "encephalomyelitis acute disseminated"

#11 MeSH descriptor Encephalomyelitis, Acute Disseminated, this term only

#12 "devic"

#13 aminopyridine*

#14 MeSH descriptor Aminopyridines explode all trees

#15 dap

#16 diaminopyridine

#17 MeSH descriptor Potassium Channel Blockers explode all trees

#18 muscle

#19 MeSH descriptor Muscles explode all trees

#20 MeSH descriptor Muscle Contraction explode all trees

#21 muscle AND contraction

#22 spinal AND cord

#23 neuromuscular AND junction

#24 MeSH descriptor Neuromuscular Junction explode all trees

#25 MeSH descriptor Neuromuscular Manifestations explode all trees

#26 motor AND endplate

#27 MeSH descriptor Motor Endplate explode all trees

#28 (#13 OR #14 OR #15 OR #16 OR #17)

#29 (#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27)

#30 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12)

#31 (#30 AND (#28 AND #29))

Appendix 2. MEDLINE (PubMed) search strategy

((((("Multiple Sclerosis"[mh]) OR ("Myelitis, Transverse"[mh:noexp]) OR ("Demyelinating Diseases"[mh:noexp]) OR ("Encephalomyelitis, Acute Disseminated"[mh:noexp]) OR ("Optic Neuritis"[mh])) OR ((("multiple sclerosis") OR ("neuromyelitis optica") OR ("transverse myelitis") OR (encephalomyelitis) OR (devic) OR ("optic neuritis")) OR ("demyelinating disease*") OR ("acute disseminated encephalomyelitis"))) AND (((randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomized[tiab]) OR (placebo[tiab]) OR (drug therapy[sh]) OR (randomly[tiab]) OR (trial[tiab]) OR (groups[tiab])) NOT ((animals[mh]) NOT ((animals[mh]) AND (human[mh]))))) AND (((aminopyridine*) OR ("Aminopyridines"[Mesh]) OR (dap) OR (diaminopyridine) OR ("Potassium Channel Blockers"[Mesh]) OR (Potassium Channel Blockers)) AND ((MUSCLE) OR (muscle AND contraction) OR (spinal AND cord) OR ("Neuromuscular Junction"[Mesh]) OR (neuromuscular AND junction) OR ("Neuromuscular Manifestations"[Mesh]) OR ("Motor Endplate"[Mesh]) OR (Motor AND Endplate)))

Appendix 3. EMBASE (EMBASE.com) search strategy

((('encephalomyelitis'/exp) OR ('demyelinating disease'/exp) OR ('multiple sclerosis'/exp) OR ('myelooptic neuropathy'/exp) OR ('multiple sclerosis':ti,ab) OR ('neuromyelitis optica':ab,ti) OR (encephalomyelitis:ab,ti) OR (devic:ti,ab)) AND (('crossover procedure'/exp) OR ('double blind procedure'/exp) OR ('single blind procedure'/exp) OR ('clinical trial'/exp) OR ('randomized controlled trial'/exp) OR (random*:ab,ti) OR (factorial*:ab,ti) OR (crossover:ab,ti) OR (cross:ab,ti AND over:ab,ti) OR (placebo:ab,ti) OR ('double blind':ab,ti) OR ('single blind':ab,ti) OR (assign*:ab,ti) OR (allocat*:ab,ti) OR (volunteer*:ab,ti))) AND (('aminopyridine derivative'/exp) OR ('4 aminopyridine'/exp) OR (aminopyridein*:ab,ti OR dap:ab,ti OR diaminopyridine:ab,ti) OR ('potassium channel blocking agent'/exp)) AND ((muscle:ab,ti OR (muscle:ab,ti AND contraction:ab,ti) OR (spinal:ab,ti AND cord:ab,ti) OR (neuromuscular:ab,ti AND junction:ab,ti) OR 'motor endplate':ab,ti) OR ('muscle'/exp) OR ('muscle contraction'/exp) OR ('neuromuscular synapse'/exp) OR ('muscle disease'/exp) OR ('nerve ending'/exp)) AND [humans]/lim AND [embase]/lim

WHAT'S NEW

Date	Event	Description
20 August 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 1, 1999
Review first published: Issue 4, 2001

Date	Event	Description
14 December 2004	New search has been performed	Searches were re-run
13 December 2004	Amended	Conclusions not changed
15 July 2002	New citation required and conclusions have changed	Substantive amendment
15 July 2002	New search has been performed	Searches were re-run

CONTRIBUTIONS OF AUTHORS

All reviewers contributed to the design of the protocol and writing of the review.
Assessment of studies and data extration was carried out by three reviewers (AS, CT, BU).

DECLARATIONS OF INTEREST

The reviewers have no known conflicts of interest.

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External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

4-Aminopyridine [*analogs & derivatives] [*therapeutic use]; Amifampridine; Cross-Over Studies; Multiple Sclerosis [complications] [*drug therapy]; Potassium Channel Blockers [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans